Discussion

In ML patients with comparable pretransplant performance status, there were no statistical differences in complications, engraftment, cell count yield, cell viability, days of apheresis, platelet transfusions, or mobilization regimen between older and younger patients receiving autografts. However, younger patients appeared to require greater RBC blood product support (p=0.05). Our data suggests that older ML patients with good performance status can be treated with autologous stem cell treatment strategies comparable to those developed for younger patients.

Variables/Age Group	Results <60 (N=23)	≥60	p-value
Age (years)	43.9 {38.7, 49.1}	62.9 {60.5, 65.3}	<.0001
Days of Apheresis	2.87 {2.33, 3.41}	2.22 {1.48, 2.97}	0.18
CD_{34} yield	5.06 {3.91, 6.20}	6.01 {3.37, 8.65}	0.28
Viability Day 1	83.8 {80.6, 87.0}	87.8 {83.4, 92.1}	0.15
Viability Day 2	84.5 {80.0, 88.2}	83.6 {74.8, 92.4}	0.76
Viability Day 3	82.9 {76.7, 89.0}	80.3 {53.5, 107}	0.57
Days to ANC Engraftment	12.7 {11.6, 13.8}	12.0 {10.3, 13.7}	0.47
Days to PLT Engraftment	15.5 {14.0, 17.0}	15.2 {13.6, 16.8}	0.75
Number of PLT Transfusions	3.17 {2.14, 4.21}	3.00 {1.41, 4.58}	0.95
Number of RBC Transfusions	3.96 {2.74, 5.18}	2.11 {1.35, 3.09}	0.05
Mobilization Regimen (%G)	57	67	0.70
Death <100 Days	4.4	0	1.00
Mucositis II-IV <30 Days	30.4	0	0.15
Sepsis <30 Days	8.7	22.2	0.56
Pneumonia <30 Days	8.7	0	1.00
Karnofsky Score	97	99	1.00

93

OUTCOME WITH A THIOTEPA CONTAINING REGIMEN AND AUTOLOGOUS HSCT IN PATIENTS WITH NHL

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Introduction: High dose chemotherapy and autologous hematopoietic stem cell rescue offers patients with advanced non-hodgkin lymphoma (NHL) a chance for long-term survival and cure. The role of thiotepa in this approach is still unknown, and little data with long-term follow-up has been published. The best chemotherapy regimen prior to stem cell infusion for patients with NHL remains unknown.

Methods/Outcome: Twenty-nine patients with advanced NHL were treated with high dose VP-16, cyclophosphamide, and thiotepa followed by autologous HSC rescue from 1993-2006. Median age was 53 (range 27-69), and all patients except 2 were beyond CR1. Overall survival and disease-free survival were 76% and 66% respectively at a median follow-up of 44 months. Five patients relapsed, with a median time to relapse of 150 days after transplant (range 82-300 days). Treatment related mortality was 10% (3/29); all 3 died from infectious complications before day 50. One patient developed treatment-related myelodysplasia.

Conclusion: An aggressive preparative regimen for autologous HSCT containing thiotepa offers patients a significant chance for long-term disease-free survival. However, caution is recommended due to early infectious complications.

94

IMMUNE MOBILIZATION OF AUTOLOGOUS PERIPHERAL BLOOD PROGENITOR CELLS: IL-2 WITH GM-CSF AND G-CSF RESULTS IN EFFECTIVE MOBILIZATION WITHOUT DELAY IN ENGRAFTMENT

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We initiated an immune mobilization trial in an attempt to mobilize cytotoxic effector cells, along with CD34+ hematopoietic progenitor cells. A Prospective Phase I trial was initiated using dose escalation of IL-2, in combination with GM-CSF and G-CSF. IL-2 began on Day 0 and continued as a daily SQ injection for 11 days. On Day 7, GM-CSF (7.5 mcg/kg/d) and G-CSF (5 mcg/kg/d) were initiated for 5 days (Days 7-11). On Day 11, leukapheresis was started if the peripheral blood CD34 + cell count was ≥ 5 cells/mcl. The endpoint of collection was $\geq 3 \times 10^6$ CD34+ cells/kg. After collection, patients received melphalan (200 mg/m^2) followed by infusion of cryopreserved stem cells. Post-transplant GM-CSF began on Day +5 and terminated once the ANC reached 5000 cells/mcl. To date, 10 patients have been treated (myeloma, n = 9; NHL, n = 1) and 9 patients are evaluable. Dose escalation of IL-2 continues since the MTD has not been reached. The first two dose levels of IL-2 have been well tolerated: Dose Level 1 (6×10^5 IU/m^2/d; n = 6 pts); and Dose Level 2 (1×10^6 IU/m^2/d; n = 3 pts). One patient has completed Dose Level 3 (1.5×10^5 IU/m^2/d) without difficulty. One patient (NHL) was removed from the study due to progressive disease. The remaining 9 patients completed the regimen. Toxicities have been mild and have included Grade 2 fever (n=1) on Dose Level 2. All patients were successfully mobilized. The median number of CD34+ cells/kg and MNC/kg collected were 3.4×10^6 (range $2.8 - 4.4 \times 10^6$/kg) and 9.5×10^8 (range $0.4 - 1.7 \times 10^9$), respectively. Two large volume leukaphereses were required (median; range 1 – 3). Following transplant, the ANC recovered on Day 13 (median; range: 10 – 14 d) and platelets recovered on Day 12 (median; range 0 – 13 d). These preliminary results demonstrate that immune mobilization and collection of an adequate number of hematopoietic progenitor cells is feasible without suppression of hematopoiesis. Toxicities are minimal but the MTD of IL-2 has not yet been reached. Post-transplant engraftment is not delayed. As patient accrual continues, we are currently evaluating the qualitative and quantitative components of the collected cells, including Th1 vs. Th2 cells and the types of dendritic cells mobilized, while evaluating lymphocyte recovery following transplant.

95

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION (AUTO-HCT) IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): RESULTS OF A SYSTEMATIC REVIEW

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Background: Despite improvements in responses, CLL remains incurable with conventional chemotherapy (CC). About 1/3 of patients are < 60 yrs, and are offered experimental therapies including high-dose chemotherapy (HDT) and auto-HCT. The objective of this study is to present the totality of the evidence by conducting a systematic review to assess the efficacy of auto-HCT in the treatment of CLL. **Methods:** A systematic search of the literature was performed using MEDLINE databases (1966- Sep 12, 2006) and handsearch of references. Included studies were prospective-randomized, non-randomized or single-arm trials. Data were extracted on primary outcomes (response rate (RR), overall survival (OS), progression-free survival (PFS) etc.). **Results:** Our search identified altogether 82 publications. Only 8 met our pre-determined inclusion criteria (table1). In this cohort of 8 trials, 2 trials were funded by public/government sources, 2 by private foundations, 1 was funded jointly by

private and public sources, and was unclear in the remaining 3. There were no randomized controlled trials evaluating auto-HCT in CLL. Five studies were single-arm trials and 3 were non-randomized trials with a control arm (autologous vs. allogeneic). Median age for pts receiving auto-HCT ranged from 45 to 59 years. When allogeneic HCT was the control arm, the median age ranged from 40 to 47 years. The cumulative number of pts receiving auto-HCT is 403 (M= 294, F= 109). Primary endpoints in the trials were: CR (clinical or molecular)= 4; OS=2; PFS=1; engraftment=1. Median clinical response rates from 6 studies ranged from 54.5 % to 89.4% at 3 to 20 months. Molecular response in one study was 76.9%. Overall survival at 3 to 6 years in 4 studies were 88.6% to 58%. Median progression-free survival in 3 studies were 92.3 % at 4 years to 30% at 6 years. **Conclusion:** The evidentiary base to recommend HDT and auto-HCT as standard practice in CLL is limited. Improved response rates, especially molecular responses are encouraging. It is uncertain whether auto-HCT is superior to CC as a salvage strategy, but data appears promising to take it to a formal testing in a randomized study.

Table 1:

Studies identified in Medline and hand-search of references (N=82)

Not included (N=74) [Reviews=18, Not clinical outcome=17, not clinical trial=13, not transplant trial=12, not CLL=8, not in English=3, prognostic-marker studies=3]

Eligible studies (N=8) [single-arm trials=5, non-randomized comparison=3]

96

AUTOLOGOUS BLOOD STEM CELL TRANSPLANTATION: REGIMEN RELATED COMPLICATIONS AND TRANSPLANT OUTCOME

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Purpose : To determine the transplant related complications after autologous peripheral blood stem cell transplantation (ASCT) and overall outcome.

Design : Cohort study of 144 consecutive patients.

Setting : A tertiary care centre

Patients and Methods : 144 consecutive patients (median age 47.5 years, range, 11 to 68 years) underwent ASCT. There were 102 males and 42 females. Indications for transplant were : multiple myeloma-78(54.2%), Hodgkin's-14(9.7%), non Hodgkin's lymphoma-14(9.7%), acute leukemia 17, CML -5(3.5%), solid tumours -16(10.7%). Patients received G-CSF mobilized peripheral blood stem cells (PBSC). All patients were treated in a single room with reverse barrier nursing without laminar air flow or HEPA filter. High dose (HD) chemotherapy was given using standard protocols . Organ toxicity was assessed according to Seattle criteria and response to transplant as per standard guidelines.

Results : 126 of 144 patients engrafted. 19 (13.2%) patients died prior to day 30. The causes of death were sepsis with or without multi-organ failure (n-12) and regimen related toxicity-7 (4.2%). Factors like poor performance status , progressive or refractory disease at transplant and failure to engraft by day 18 were associated with increased risk of day 30 mortality. GIT toxicity, mucositis, veno-occlusive disease, liver and renal dysfunction were main regimen related toxicities; GIT toxicity and mucositis was significantly higher among patients who received HD melphalan for conditioning. Post transplant, CR rate was significantly higher in chemosensitive disease group (70%) compared to 20% in chemo-refractory disease, $p<.01$. The median overall survival (OS) for all patients is 55 months ± 9.07(CI 37.22-72.78) with estimated OS at 2 and 5 years being 66.5% and 45%, respectively. Event - free survival (EFS) for the whole group is 24 months ± 5.13(13.94-34.06) with probability of EFS 2 and 5 years being 47.2 %, and 41%, respectively . Survival was significantly better for patients with chemo-sensitive disease at transplant (median OS 89 months vs 18 months,$p<.0001$). Patients who were in CR post transplant had a significantly better overall survival . Currently, 60 of 126 patients (47.6%) are alive at a median follow up of 3 years. 66 patients have died predominantly due to relapse - 57/66 (86.4%).

Conclusion : Good primary pre-transplant management and careful case selection are two important factors associated with good transplant outcome.

97

RITUXIMAB-RELATED LATE-ONSET NEUTROPENIA AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION FOR MALIGNANT LYMPHOMA

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Rituximab (Rit) chimeric human/mouse monoclonal antibody directed against the CD20 antigen. It can be used before stem cell harvest as a way of in vivo purging or after stem cell transplantation as an adjuvant therapy.

Recently, several cases of late-onset neutropenia (LON) have been described in relation to its utilization in stem cell transplantation as well as chemotherapy setting.

The reason why Rit induces neutropenia was poorly understood. Dunleavy reported that perturbation of SDF-1 during B-cell recovery retards neutrophil egress from the bone marrow as a mechanism of Rit-induced neutropenia (Blood, Vol. 106, 795-802).

We retrospectively analyzed the incidence of LON in autologous peripheral blood stem cell transplantation (autoPBSCT) for malignant lymphoma (ML) using Rit, autoPBSCT for ML without Rit, and autoPBSCT of CD34+ cells for refractory autoimmune disease (AD).

Methods

LON was defined as neutrophil count less than 1,000/μl after achieving durable hematopoietic engraftment without apparent reasons including myelotoxic drug, viral infection, or disease progression. The hematologic data of out patient clinics were retrospectively analyzed.

Results

The incidence of LON was 64.3% in autotransplanted ML with Rit. The Nadir of LON was 69-751 (median 578) /μl. The onset of LON from transplant was 61-128 (median 80) days. The duration of LON was 14-124 (median 56) days. There were no LON-related infectious complications.

The incidence of LON of autotransplanted ML without Rit and autotransplanted AD was 8.3%, and 10%, respectively.

Conclusion When Rit was used peri-autotransplant period, the incidence of LON was increased. Since autotransplantation with purified CD34+ cells did not increase the incidence of LON, our analysis results could not support the idea that perturbation of SDF-1 during B-cell recovery retards neutrophil egress from the bone marrow as a mechanism of Rit-induced neutropenia.

	Results		AD using CD34+ cells (n=10)
	ML with Rit (n=14)	ML without Rit (n=12)	
age(median)	14-59(54)	31-68(50)	21-63 (54)
sex (M/F)	7 / 7	10 / 2	3 / 7
disease	DLBL 12, FL 2	DLBL 6, PTCL 2, LBL 1, MCL 1, 2	SSc 7, SLE 1, DM/IP 1, WG 1
disease status	ICR 11, IRel 2, 2CR 1	ICR 8, IPR 2, Ref 2	
No. of infused CD34+ cells	7.4 (3.9 -13.9) ×10e6/kg	8.3 (1.4-24.5) ×10e6/kg	4.9 (2.0 -16.0)) ×10e6/kg
Conditioning	R-MCEC 10, MCEC 3, 2	MCEC 10, TBI 1, 1	HD-CY
LON	9 (64.3%)	1(8.3%)	1(10%)
Neutoropenia of known reason	VZV 2	Drug 1	CMV 1
observation period (median)	121-929 (276)	148-1715 (860)	